

New Methods

Time to Onset of Regional Relaxation: Feasibility, Variability and Utility of a Novel Index of Regional Myocardial Function by Strain Rate Imaging

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OBJECTIVES	Time to onset of regional relaxation (T_R) has been proposed as a novel index of regional myocardial function. This study sought to prospectively establish the feasibility and variability of T_R in healthy volunteers (CONTROL) and to examine its utility in patients with inducible ischemia (PATIENT).
BACKGROUND	Strain rate imaging (SRI) depicts myocardial deformation and enables quantitation of regional myocardial function with high temporal and spatial resolution. Thus, regional mechanical events can be accurately timed with SRI. The time point of regional transition from contraction to relaxation is altered in pathologic states.
METHODS	Resting mean segmental T_R was determined in 60 subjects: 20 in the CONTROL group and 40 in the PATIENT group. T_R was also measured at peak dobutamine stress in the PATIENT group. An automated image analysis program determined the time point of transition from regional contraction to relaxation activity, and calculated T_R , defined as the time, in milliseconds, from the electrocardiogram R-wave to this transition point.
RESULTS	Automated T_R measurements were feasible in more than 90% of the segments in CONTROL and PATIENT groups. Mean T_R was 353 ± 24 ms and was shorter in the mid segments compared to apical and basal segments. Intra- and interobserver variability were low (6% and 9%, respectively). In the PATIENT group, the percent decrease in T_R during dobutamine stress was significantly higher in normal compared to ischemic segments (30% vs. 19%, respectively, $p = 0.01$). A percent change $>20\%$ in T_R identified patients with an ischemic response during dobutamine infusion (sensitivity 92%, specificity 75%).
CONCLUSIONS	T_R , a novel quantitative index of regional myocardial function, can be determined with low variability and satisfactory feasibility in routine clinical settings. Percent change in T_R identifies ischemic segments during dobutamine stress echocardiography (DSE) and may allow quantitative assessment of DSE. (J Am Coll Cardiol 2002;39:1531-7) © 2002 by the American College of Cardiology Foundation

Quantitation of regional myocardial function would greatly enhance the value of the current echocardiographic examination. Tissue Doppler imaging (TDI), which tracks local myocardial tissue velocities with high temporal and spatial resolution, has enabled online quantitation of regional myocardial function (1-5). However, TDI can be adversely influenced by translational motion of the heart and may not distinguish between contracting and tethered myocardium. Strain rate imaging (SRI) uses tissue velocity data to calculate regional deformation rates and is less influenced by translational motion or tethering (6-9). Thus, SRI may be superior to TDI in regional function analysis. However, Doppler parameters are influenced by the insonating angle, lack target tracking and have low volume resolution. Therefore, high-resolution regional tracking of temporal events, which are less affected by these limitations, appear promis-

ing. Angiocardigraphy and radionuclide angiography, techniques also used for quantitative cardiac function analysis, lack the temporal and spatial resolution necessary to track the rapid events of the cardiac cycle. In contrast, SRI can reliably track regional myocardial contraction and relaxation activity with high temporal resolution.

The initiation of diastole is a sensitive, energy-dependent phase of the cardiac cycle (10). The transition from systole to diastole is negatively influenced by the lack of adenosine triphosphate (ATP), which delays the onset and rate of relaxation in conditions such as ischemia. Ischemia-induced diastolic asynchrony or delay in the onset of regional relaxation has been demonstrated in animal and clinical models (11-15). We have recently demonstrated a quantifiable delay in the time to onset of regional relaxation by SRI in an animal model of coronary occlusion (16,17).

We have proposed time to onset of regional relaxation (T_R) as a novel parameter of regional myocardial function (18). To extend the application of this parameter, we prospectively established feasibility and variability of T_R in

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Abbreviations and Acronyms

ATP	=	adenosine triphosphate
CAD	=	coronary artery disease
DSE	=	dobutamine stress echocardiography
SRI	=	strain rate imaging
TDI	=	tissue Doppler imaging
T _R	=	time to onset of regional relaxation

healthy volunteers and examined the utility of T_R in detecting inducible ischemia during dobutamine stress.

METHODS

Study population. This study was approved by the Institutional Review Board. Healthy volunteers (CONTROL group) were imaged to establish feasibility and variability of T_R. Volunteers had a low probability of coronary artery disease (CAD) because of the absence of chest pain and fewer than three risk factors, including history of smoking, diabetes, hypertension, hypercholesterolemia and ST-T abnormalities on electrocardiogram (ECG) (19,20). Consecutive patients (PATIENT group), 18 years or older, referred for a clinically indicated dobutamine stress echocardiogram (DSE) were studied to evaluate the utility of T_R in detecting inducible ischemia.

Exclusion criteria were unstable angina, New York Heart Association class III or IV symptoms, recent myocardial infarction (<4 weeks), atrial fibrillation, frequent and complex ventricular ectopy, hypertrophic cardiomyopathy, significant aortic stenosis (valve area <1.0 cm² or peak velocity >4 m/s), hemodynamic instability (systolic blood pressure <90 or >180 mm Hg and heart rate <40 or >120 beats/min) and suboptimal image quality with inadequate endocardial definition in two or more segments.

Dobutamine stress echocardiogram. A dobutamine atropine stress echocardiogram was performed according to standard protocol, using 3-min stages, a maximum dose of 40 μg/kg per min and atropine (maximum dose 2 mg), as needed, to achieve 85% of age-predicted maximum heart rate (21).

Image acquisition sequence. Imaging was performed using a 2.5 MHz phased array transducer with a System FiVe ultrasound machine (GE Medical Systems, Milwaukee, Wisconsin). For interpretation of the DSE, standard parasternal short- and long-axis and apical four- and two-chamber views were acquired at baseline and at each stage. Tissue Doppler images were acquired using three standard apical projections (apical four-, two- and long-axis). Single walls were imaged using a narrow-angle sector (30°) and high frame rates (100 ± 16 frames/s). Three cardiac cycles were captured per projection at baseline and peak stress, and stored on a magneto-optical disk.

DSE analysis. Segmental wall motion analysis was performed by experienced blinded readers using a standard 16-segment model (22). Segments were designated as nor-

mal, ischemic or infarct on the basis of the stress response. The development of new or worsening wall motion abnormalities at any stage of stress in one or more segments was considered an ischemic response. Segments that were akinetic or hypokinetic at baseline and peak stress, were classified as infarct and were excluded from analysis. For T_R analysis, segments from patients with no ischemic response were classified as normal, and segments with ischemic response by visual wall motion analysis were classified as ischemic.

T_R ANALYSIS. Image analysis was performed offline at a PC workstation using custom analysis software (TVI version 6.3, GE Vingmed, Horten, Norway). A line of interest was placed at the mid myocardial level using the curved M mode function of the TVI program. This resulted in a strain rate color map of local myocardial activity displayed in color code (Fig. 1). Myocardial shortening (contraction) and lengthening (relaxation) were coded as yellow-red and blue-white, respectively. In the normal strain rate tracing, the systolic strain rate has negative polarity and is represented by a wave below the zero line, whereas the opposite occurs with diastolic strain rates (Fig. 1). Therefore, the transition from contraction to relaxation activity in a particular myocardial segment is denoted by the time point at which the strain rate profile crosses the zero line from negative to positive polarity or when the color map changes from yellow-red to blue-white. We defined T_R as the time from the R-wave of the ECG trace to this transition point (Fig. 1). Curved anatomic M-mode analysis was performed on each wall in the apical long, apical four-chamber and apical two-chamber views and segmental T_R was determined using the ASE 16-segment model. Images were saved as Matlab files and then exported to a custom semiautomated Matlab based image analysis program (GE Vingmed, Horten, Norway). This program automatically determines the point at which the strain rate profile switches polarity from negative to positive for each pixel line, and calculates mean T_R for each echocardiographic segment. The T_R value was corrected for the heart rate using Bazett's formula and expressed in milliseconds (23). Mean T_R for each segment was derived by averaging values from three separate cardiac cycles. Segments were excluded from analysis if the automated program was unable to provide a number or if the image quality was deemed poor by the observer.

For intraobserver variability, the same observer determined T_R using the automated program on two images acquired at separate points in time in the same projection for the same individual. For interobserver comparisons, two independent observers analyzed the same image.

STATISTICS. Continuous variables are expressed as mean ± SD. Difference in T_R values between groups was tested using a two-tailed *t* test. Analysis of variance with Bonferroni correction was used to compare more than two groups. Inter- and intraobserver variability were expressed as coef-

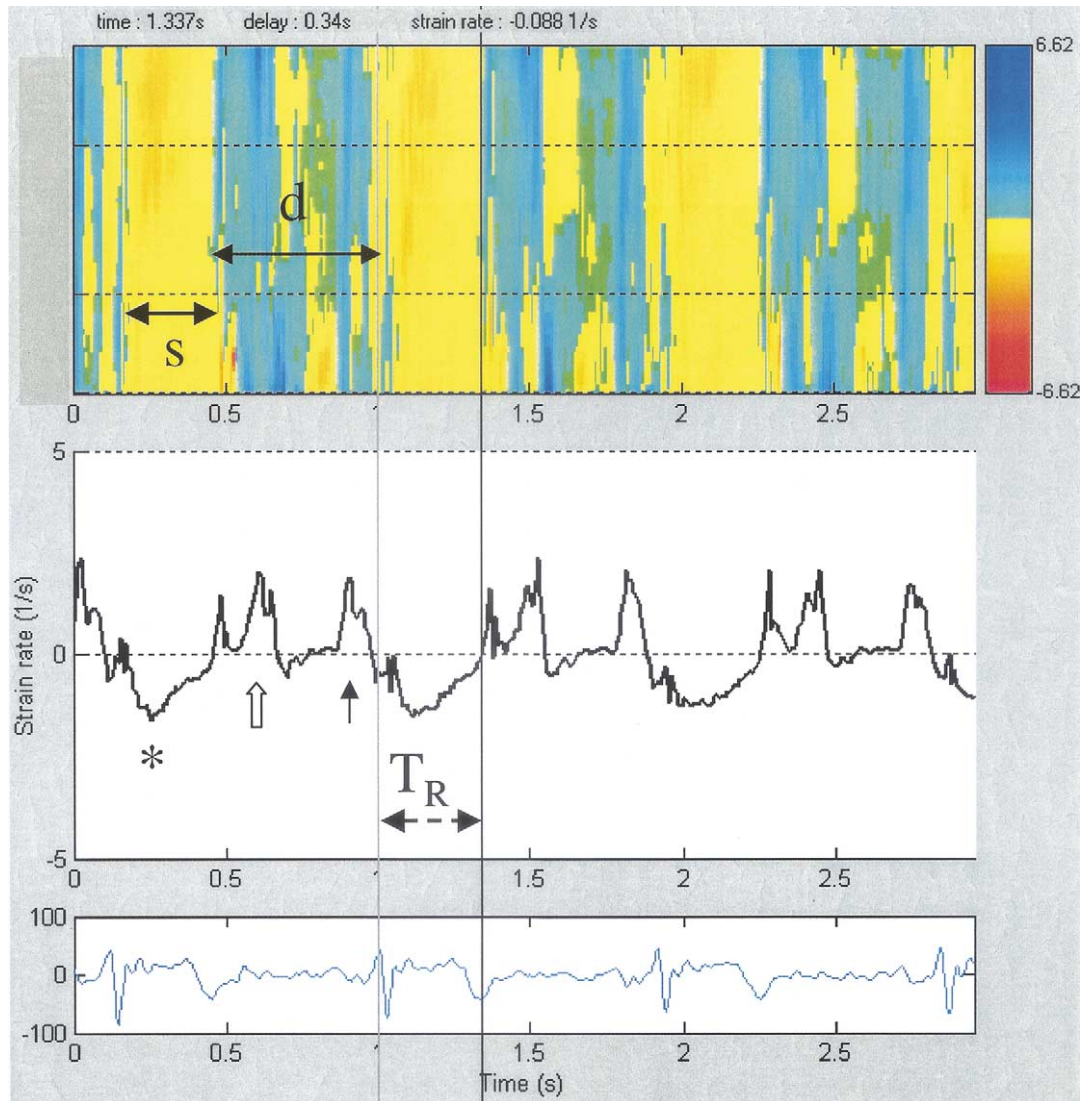


Figure 1. Top panel illustrates the color M-mode image, with **yellow** indicating systolic shortening (s) and **blue-white** indicating diastolic lengthening (d) in strain rate imaging. The time point of transition from shortening to lengthening (contraction to relaxation) is indicated by the **solid black line**. The **middle panel** shows the strain rate tracing, * = systolic wave; **solid arrow** = late diastolic wave; **open arrow** = early diastolic wave. The **lower panel** is the electrocardiogram trace. An example of the time to onset of relaxation (electrocardiogram R-wave to the transition point) is illustrated at the bottom of the strain rate tracing (T_R). The **dotted lines** separate the septum into apical (**top**), mid and basal segments.

ficient of variation (standard deviation expressed as a percentage of the mean value). For patients undergoing DSE, ROC analysis was performed to determine the change in T_R that best differentiated those with and without ischemia. Sensitivity and specificity were expressed using patients, rather than segments, as the unit of analysis. Abnormality in one or more segments by T_R was considered as an ischemic response. A kappa statistic was generated to test concordance between DSE and T_R for recognition of ischemia. A p-value of <0.05 was considered significant.

RESULTS

There were 20 subjects in the CONTROL group and 40 subjects in the PATIENT group (Table 1).

Feasibility. Imaging time ranged between 1 and 4 min per subject (per stage) in the CONTROL and PATIENT

groups. Offline image processing and automated T_R calculation took 7 to 10 min per subject per stage. Automated T_R measurements were possible in 299 of 320 (93%) segments in the CONTROL group and in 576 of 640 (90%) segments in the PATIENT group.

Mean T_R . CONTROLS. Mean T_R values for each echocardiographic segment in healthy volunteers are presented in Table 2. Mean T_R was shorter in the mid segments compared with apical segments (344 ± 23 ms vs. 360 ± 33 ms, $p = 0.001$) with a trend toward a shorter T_R ($p = 0.06$) in the mid segments compared with the basal segments (354 ± 26 ms). There was no statistical difference in mean T_R between the basal and apical segments ($p = 0.2$). Mean T_R of the same segments, measured from two separate images by the same observer, were statistically similar ($p = 0.4$), with a mean difference of 4 ± 33 ms and

Table 1. Baseline Characteristics of Subjects

	Volunteers (n = 20)	Normal Patients (n = 14)	Ischemic Patients (n = 26)
Age (yrs)	32 ± 9	57 ± 10*	67 ± 12*
BSA (m ²)	1.73 ± 0.2	1.74 ± 0.3	1.81 ± 0.2
SBP (mm Hg)	112 ± 15	131 ± 31	138 ± 29
HR (beats/min)	70 ± 9	78 ± 13	73 ± 15
Chest pain (%)	0	6 (43)	23 (88)
Men (%)	65	53	68
DM (%)	0	0	5 (19)
HTN (%)	0	3 (21)	11 (42)
CAD (%)	0	0	6 (23)

*p < 0.05.

BSA = body surface area; CAD = previous history of coronary artery disease or myocardial infarction; Chest pain = typical or atypical angina; DM = diabetes; HR = heart rate, HTN = hypertension; SBP = systolic blood pressure.

intraobserver variability of 6%. Similarly, there was no statistical difference in mean T_R measurements between two independent observers who analyzed the same images (mean difference 5 ± 27 ms [$p = 0.2$], and interobserver variability 9%).

PATIENTS. Fourteen of 40 patients who underwent DSE had normal segmental wall motion at baseline and peak stress (normal group). All in this group had low pretest probability of CAD according to the same criteria established for volunteers. With stress, ischemia was present in 26 patients (ischemic group). Patients in both groups were similar with respect to proportion of men, peak dobutamine dose, total atropine dose and peak heart rate, although the ischemic group tended to be older ($p = 0.03$).

SEGMENTAL ANALYSIS AND CORRELATION WITH DSE. Of the 576 segments acceptable for automated T_R analysis, 158 had an ischemic response, 348 had a normal response and 70 had baseline wall motion abnormalities and were not analyzed. Baseline T_R values were similar in ischemic and normal segments (409 ± 67 and 410 ± 55 , $p = \text{NS}$). With dobutamine infusion there was a significant decrease in segmental T_R in normal segments. The absolute difference between baseline and peak T_R was higher in normal than ischemic segments (124 ± 70 vs. 54 ± 70 , $p < 0.01$) (Fig. 2). The percent decrease in T_R , that is, the change in T_R normalized for the baseline T_R , was larger in normal ($34\% \pm 10\%$) than in ischemic segments ($12\% \pm 18\%$), $p < 0.01$ (Fig. 3). A cutoff of 20% decrease in T_R with dobutamine yielded a sensitivity of 92% (24 of 26 patients) and specificity of 75% (10 of 14 patients) for dobutamine-induced wall motion abnormality. Concordance between

DSE and T_R for recognition of ischemia was good (kappa statistic 0.7).

DISCUSSION

Mean T_R has low variability among healthy volunteers and can be measured in a simple and timely fashion in routine clinical settings. During dobutamine infusion, percent decrease in T_R was higher in normal compared to ischemic segments.

Regional myocardial function assessment. Quantitative assessment of regional myocardial function has been the objective of several innovative technologies in echocardiography (24). Tissue Doppler imaging and SRI by depicting regional mechanical activity with high temporal and spatial resolution may provide information regarding systolic and diastolic function of the heart. In regional pathologies, TDI, which measures tissue displacement from a single point along the ultrasound beam, may be imprecise because it can be adversely influenced by translational motion of the heart and by myocardial tethering (25). On the other hand, SRI calculates velocity gradients between two distinct points along the ultrasound beam and is less susceptible than TDI to translation and tethering artifacts. "Shortening," which occurs when the two points are moving toward each other, can be used to describe the contraction properties; "lengthening," when the two points are moving away from each other, can be used to describe the relaxation properties of a specific region of the myocardium. Regional myocardial function evaluation by SRI can thus be performed by measuring strain rate amplitudes or by timing reciprocating events within the cardiac cycle.

Timing versus amplitude. Strain rate profiles tend to be noisy and measurement can be challenging. Furthermore, strain rate amplitudes vary with insonating angle (26). In contrast, phase changes are easier to measure and are less dependent on the insonating angle or image quality than on peak amplitude. The high temporal resolution in SRI can accurately determine regional phase changes from contraction to relaxation patterns and vice versa. Nonuniformity of regional relaxation has been demonstrated in ischemic myocardium (11,12,14,15,27,28). Thus a simple parameter such as the segmental time to onset of relaxation (T_R) will be able to identify a segment wherein relaxation starts later than other segments. This parameter would be objective, quantitative, less angle-dependent and therefore more robust than peak amplitude of strain rates or strain in the assessment of regional myocardial function. A delay in

Table 2. Mean Segmental T_R in Healthy Volunteers (CONTROL Group)

	Anterolateral	Inferoseptal	Inferolateral	Anteroseptal	Inferior	Anterior
Apical	357 ± 25	360 ± 28	—	—	379 ± 43	358 ± 29
Mid	364 ± 24	338 ± 13	338 ± 13	340 ± 20	361 ± 37	351 ± 21
Basal	350 ± 29	350 ± 31	365 ± 28	355 ± 30	358 ± 15	339 ± 13

Values are corrected for heart rate and presented in milliseconds.
 T_R = time to onset of regional relaxation.

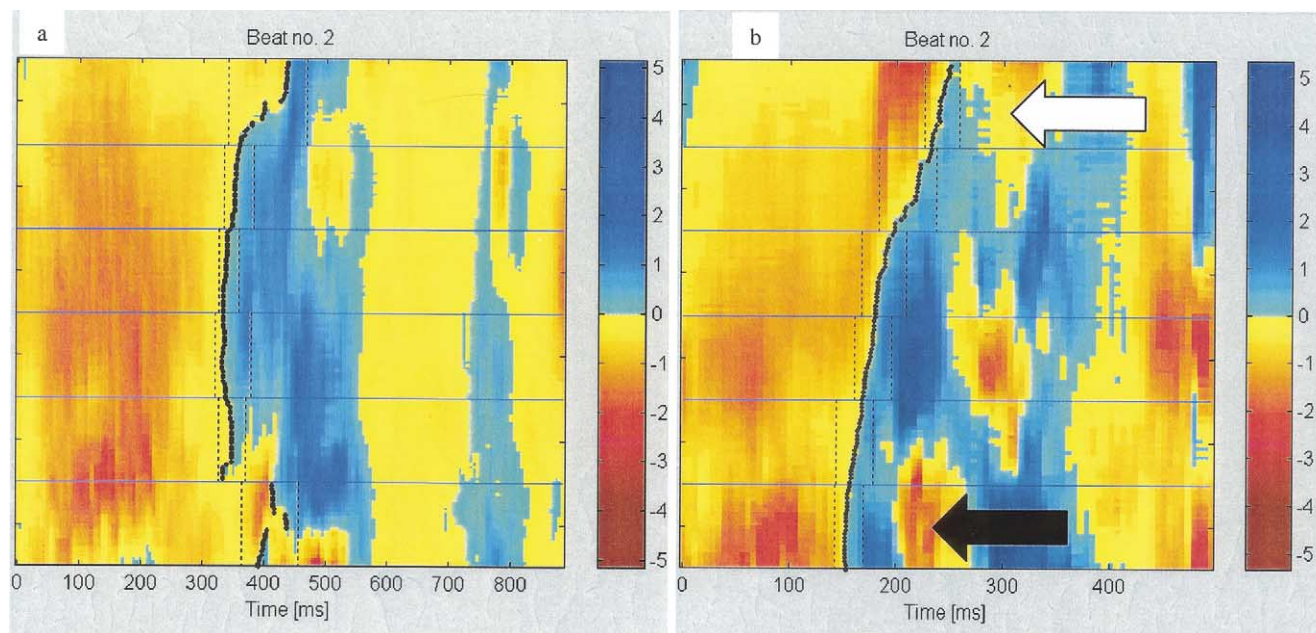


Figure 2. Strain rate color M-mode image illustrating a decrease in T_R from baseline (a) to peak stress (b) in the nonischemic basal segment (black arrow), and minimal T_R change in the ischemic apical segment (white arrow). T_R = time to onset of regional relaxation.

regional isovolumic relaxation time and time to peak velocity has been previously demonstrated using TDI during dobutamine stress (29). However, as alluded to earlier, TDI may not be the optimal method of assessing regional function.

Key events in the cardiac cycle. The transition from systole to diastole and vice versa delineates a phase change in the mechanical activity of the heart. The transition to relaxation is contingent upon the removal of calcium ions from the cytosol, which is an energy-dependent process (30). Ischemia-induced ATP deficiency may lead to delayed onset of relaxation reflected by prolonged T_R (31-35).

Prolongation of T_R . The mechanisms of T_R prolongation in ischemia are uncertain. However, possible explanations include post-systolic shortening, delayed local activation and transmural conduction delays (28,36).

Feasibility and normal values. In this study, mean T_R was measured easily and in a timely fashion in normal volunteers and patients reporting for stress echocardiography. Strain imaging would add approximately 4 min to the routine echocardiographic examination, when only apical views are examined. The automated program was able to determine segmental T_R values in most (93%) segments in both subject groups. Mean T_R values were consistent within basal, mid

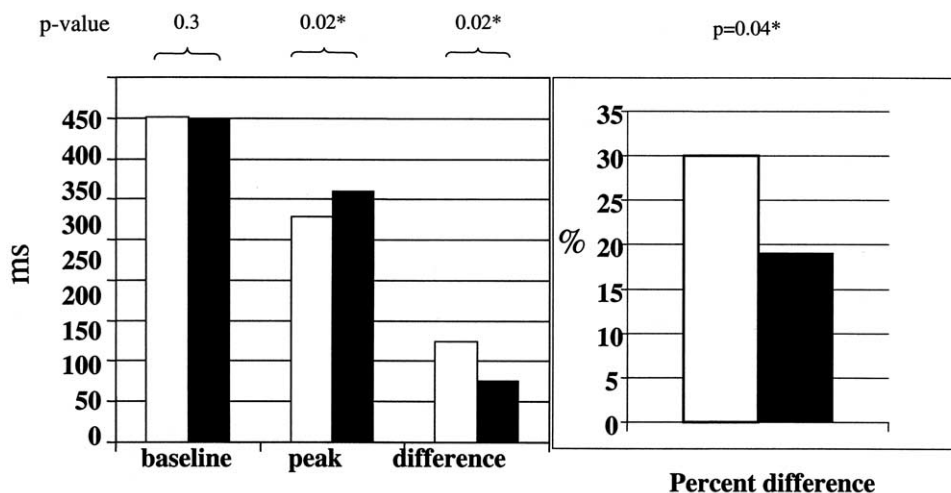


Figure 3. Plot demonstrating no difference in baseline T_R between normal (white bars) and ischemic (black bars) segments, a longer T_R at peak stress and a smaller difference between peak and baseline T_R in ischemic segments compared with normal segments (left). The percent change in T_R (peak vs. baseline) normalized to baseline T_R was significantly higher in normal (30%) compared to ischemic (19%) segments (right). * $p < 0.05$. T_R = time to onset of regional relaxation.

and apical segments. There was a shorter T_R in the mid segments, specifically the mid-septal segment, probably reflecting early septal activation. Intra- and interobserver variability was low. The temporal resolution in this study was ~ 10 ms based on an average image acquisition rate of 100 frames/s. In our experience, optimizing the grayscale image quality, imaging a single wall at a time, using high frame rates and a narrow angle sector greatly enhanced image quality and facilitated automated T_R analysis.

Previous experiments in a porcine model of acute coronary occlusion demonstrated a prolongation in resting T_R with ischemia (16,17). Analysis of changes in this novel parameter of regional relaxation has not been reported in inducible ischemia during dobutamine stress. In our study, T_R uniformly decreased with increasing stress in the normal segments. This response was significantly blunted in ischemic segments.

Dobutamine has been shown to decrease time to onset of relaxation and increase relaxation rates (37). Thus, our data indicating a decreased T_R during dobutamine are concordant with previous studies. In ischemic segments, there is little or no change in T_R with dobutamine, suggesting a slowing or delay in onset of early relaxation. In this study, normal segments had a decrease in T_R of $\geq 20\%$ with dobutamine. Data from this study would allow prospective testing of various cutoff points in larger studies, with an independent gold standard for CAD such as angiography or nuclear perfusion scans.

Study limitations. In this study, regional time to onset of relaxation was not confirmed using an independent technique. Only apical views were examined and T_R measurements were made only along the longitudinal plane. Preliminary data from our laboratory indicate that there is minimal T_R variation between longitudinal and radial orientation of the walls. Because T_R is a time interval, its variability in conduction abnormalities and arrhythmias will have to be investigated. The analysis of inducible ischemia used visual wall motion score to define an ischemic segment. Nuclear perfusion scans and angiography would provide independent assessment of ischemia. However, there are inherent problems with comparing cellular perfusion to segmental motion, and determining the segmental extent of angiographic disease remains arbitrary and vague. We excluded segments that demonstrated a baseline wall motion abnormality. Our study was powered to study differences between normal and abnormal response in segments with normal wall motion at baseline. In order to examine changes in T_R in segments with wall motion abnormality at baseline, we would need to evaluate baseline variability in this group. This would require larger numbers to demonstrate statistical differences between peak and baseline T_R .

Conclusions. T_R , a novel quantitative index of regional myocardial function, demonstrates low variability and satisfactory feasibility in routine clinical settings. Decrease in T_R was significantly higher in normal segments compared to segments with an ischemic response on DSE. Evaluation

in larger populations will determine the clinical impact of this new quantitative index.

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